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Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research

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This paper evaluates the current epidemiological literature examining the possible relationship between exposure to environmental tobacco smoke ("ETS") and cardiovascular disease. Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. This paper evaluates seven studies that examine this issue (table 8–1). Five of the studies are prospective in nature, one is a case-control design (retrospective), and one is an experimental design examining the biological plausibility of a link between ETS and cardiovascular disease.

Several key points of epidemiology need to be mentioned here, and should be kept in mind when reading the critiques of the seven studies. To prove causality five criteria need to be met. The first relates to the strength of the association. There are three elements to this criterion. First, there must be a statistically significant increase in the incidence of the disease in the exposed population compared with the non-exposed population. Second, for the association to be regarded as meaningful, a relative risk of 2.0 or greater is generally considered necessary. Third, the association should also be dose dependent, i.e., higher doses are associated with higher incidence of disease.

The second point is that consistency of the association must exist among the relevant studies. This means that similar rates of disease must occur at different times and places, under comparable study designs.

A third point deals with the temporal aspect of the association. This means that exposure to ETS should have occurred at a reasonable time before the onset of disease, given what is known about how long it takes for cardiovascular disease to develop.

A fourth point is specificity of the association. With ETS, this means that exposure to ETS must be shown to be associated with cardiovascular disease while controlling for all confounding variables.

Table 8–1
Environmental Tobacco Smoke and Cardiovascular Disease

	Design	*Findings*	*Methodological Problems*
1. Hirayama (1981, 1984)	Sixteen year prospective study of nonsmoking Japanese women classified at start of follow-up by the smoking status of their husbands. 142,857 women 40 and over (91,540 nonsmoking wives).	1. Relative risk of 1.31 for ischemic heart disease for nonsmoking women whose husbands smoked > 19 cigarettes per day compared with nonsmoking women whose husbands did not smoke. 2. Mantel-Haenszel significant at $p < .019$, 1984. 3. "Passive smoking did not seem to increase the risk of developing . . . ischemic heart disease." –Hirayama, 1981.	1. Potential biases. 2. Misclassification of smokers and non-smokers. 3. Misclassification of dose response (number of cigarettes smoked per day). 4. Looked at spouse exposure only, not workplace. 5. No control for indoor air pollution, e.g., cooking with kerosene stoves. 6. Not representative of Japanese population—only agriculture represented. 7. Non-random sample of prefectures—only a convenience sample.
2. Garland (1985)	Prospective—enrolled 82% of adults ages 50–79 between 1972–1974 in a community in San Diego. Blood pressure and plasma cholesterol measured at entry; interviewed all cohort of 695 current married non-smoking women free of heart disease; ten year follow-up.	1. Elevated cardiac disease deaths in non-smoking women, ages 50–79, whose husbands were former or current smokers. 2. 19 deaths from ischemic heart disease after ten years.	1. Some misgrouping—wives of former smoker were grouped with wives of current smokers. 2. Small sample sizes, value may be inappropriate based on Mantel-Haenszel, and may only be an approximation; still p was only $p < .10$. 3. 15 of 19 deaths occurred in nonsmoking women married to former smokers—puzzling results.
3. Gillis (1989)	Two urban communities in Scotland. Ten year follow-up report. 8,128 adults ages 45–64.	Non-smokers exposed to cigarette smoke in their homes had a slightly higher rate of myocardial infarction than those unexposed.	1. Small sample size. 2. Few of the results were statistically significant.

Table 8–1 continued

	Design	*Findings*	*Methodological Problems*
4. Svendsen (1987)	1. Multiple Risk Factor Intervention Trial (MRFIT). 2. Randomized primary prevention trial designed to test the effect of a multifactor intervention program on mortality from coronary heart disease in men with previous cardiac episodes. 3. Men were chosen for participation if they had at least two of three risk factors for heart disease (smoking, high cholesterol levels, high blood pressure).	1. No difference between smoking wives and nonsmoking wives for non-smoking men for blood pressure or cholesterol. 2. Roughly two-fold increase in risk of CHD mortality and morbidity among nonsmoking men exposed to ETS of wives.	1. Sample size small. 2. Results—not statistically significant.
5. Helsing (1988)	1. Twelve year study executed in Washington County, Maryland. 2. July, 1963 census of 91,909 people. 3. Whites only. 4. Death certificates collected from July, 1963 through July, 1975. 5. Non-smokers, ages 25 and over. 6. 4,162 men and 14,873 women.	1. Death rates from arteriosclerotic heart disease were higher among men (Relative risk = 1.31) and women (relative risk = 1.24) who lived with smokers in 1963, after adjustment for age, marital status, years of schooling, and quality of housing index. 2. For women, relative risk increased significantly ($p < .005$) for dose response (increasing levels of exposure). 3. Men—little evidence of a dose response relationship.	1. Only smoking data collected on every person was in 1963. 2. No measurement of changes in smoking habits. 3. No data on household changes from 1963–1975. 4. Very little other risk factor data for heart disease. 5. No diet, exercise, blood pressure, cholesterol data, or ETS exposure out of home.

Table 8–1 continued

	Design	*Findings*	*Methodological Problems*
6. Lee (1986)	Case-control.	Ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to involuntary smoking, based on smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure.	Case-control methodological issues.
7. Aronow (1978)	Experimental design.	ETS aggravates angina pectoris.	1. Endpoint of angina based on subjective evaluation. 2. Stress not controlled for.

The fifth point is that there must be biological plausibility. This means that under experimental conditions exposure to the pertinent substance (or similar substances) must be shown to cause biological changes that can lead to the disease in question.

All five conditions must be met for causality to be established. We will return to these points at the end of the paper, when we examine recommendations for future research.

I. Summary of Epidemiological Literature

A. Prospective Studies

1. Hirayama. Hirayama (1984) conducted a prospective cohort study in 29 health center districts in six prefectures in Japan between January 1966 and December 1981. In total, 265,118 adults (122,261 men and 142,857 women) aged 40 years and over were followed. Ninety-five percent of the census population was interviewed between October and December 1965. Also, Hirayama established a record linkage system under which he gathered and analyzed death certificates, risk factor records, and a residence list obtained by an annual census. Questions on smoking habits were asked independently of husbands and wives at the beginning of the study. There were 91,540 nonsmoking married women whose husbands' smoking habits were reported by questionnaire.

In 1981, Hirayama (1981) concluded that "husbands' smoking habits seemed to have no effect on their non-smoking wives' risk of developing ischemic heart disease." Hirayama reported age/occupation standardized risk ratios for ischemic heart disease in non-smoking women by smoking habit of husband. When the husband was a non-smoker, the relative risk was 1.0. When the husband was an ex-smoker or smoked 1–19 cigarettes per day, the relative risk was .97. When the husband smoked 20 or more cigarettes/day, the relative risk was 1.03, and the reported p value was not significant at 0.393.

Hirayama (1984), in a 1984 paper, reported an elevated risk of ischemic heart disease morbidity based on further analyses. The relative risk for non-smoking married women for husbands who were non-smokers was 1.0; for husbands who were ex-smokers or smoked 1–19 cigarettes/day the relative risk was 1.10; and for husbands who smoked 20 or more cigarettes per day, the relative risk was 1.31, with a 90% confidence interval of 1.06 to 1.63. The reported p value was significant at .019.

Hirayama's study has several major methodological problems. The first problem is potential misclassification of smokers and non-smokers. Many of the wives who stated they were non-smokers may in fact be ex-smokers or even current smokers, and thus likely to have had or continue to have direct (as opposed to indirect) exposure to cigarette smoke.

The second problem is that Hirayama's study included a disproportionate number of women of lower socioeconomic status. In Japan, these women live in much closer proximity to their cooking quarters and may have more exposure to charcoal or kerosene stoves than women of higher socioeconomic status. This exposure has been associated with lung cancer in women in Hong Kong. Women in Japan of a higher socioeconomic status live farther away from their kitchens and are more likely to use electric burners. The Hirayama study failed to control for these confounding variables, which may be associated with ischemic heart disease.

A third problem is the misclassification of dose response. Ex-smoking husbands were lumped with current cigarette smokers of 1–19 cigarettes/day. Because ex-smokers are very different in their cigarette exposure rates and lifestyles than smokers of 1–19 cigarettes/day, this could skew the data.

A fourth problem is that Hirayama only examined the exposure of the wife in the context of the husband's cigarette smoking behavior. No attempt was made to quantify any exposure to ETS outside of the home, such as in the workplace.

A fifth problem is that the Hirayama study was not representative of Japanese society but only of an agriculturally based population, which is not typical for Japan. In addition, six prefectures were chosen to participate in the study based on the fact that they appear to have had the best conditions for collecting data. Hence, random sampling was not used.

A sixth problem is that the Hirayama study did not control for other risk factors associated with cardiovascular disease, i.e., systolic blood pressure and plasma cholesterol.

Although the Hirayama study offers a large prospective cohort to examine the relationship between presumed exposure to environmental tobacco smoke and ischemic heart disease, one can not draw definitive conclusions because of the aforementioned methodological problems.

2. **Garland.** Garland (1985) conducted a prospective cohort study commencing in 1972–1974 in Rancho Bernardo, a white middle-class suburb of San Diego, California. The entire adult population was invited to participate, of which 82% agreed. The authors report that the respondents were representative of the total population with regard to age and sex.

All respondents were administered a standardized inventory, including questions about age, cigarette smoking, history of past hospitalizations for heart attack, heart failure or stroke, and number of years married. Cigarette smoking was assessed as current, former or never. Only current smokers were asked the number of cigarettes they smoked per day. No data were obtained for duration of smoking. In addition, blood pressure and plasma cholesterol were obtained.

An annual mailing was utilized to determine vital status for the next ten years. Death certificates were obtained for all decedents. Diagnosis of ischemic heart disease was validated by interviews with family and physicians, and/or examination of hospital records, for 85% of the deceased group.

Six hundred ninety-five (695) currently married nonsmoking women, ages 50–79, with no previous history of heart disease or stroke were followed based on their husband's self-reported smoking status in 1972–1974.

The results, after adjusting for age, systolic blood pressure, total plasma cholesterol, obesity index and years of marriage gave a relative risk of 14.9 of deaths from ischemic heart disease for women married to current or former smokers at entry compared with women married to never smokers. The p value was not significant, $p \leq .10$.

Important methodological problems exist with the Garland study. The first is that Garland later reported a corrected relative risk of 2.7 (not 14.9 as reported in the 1985 publication). The p value is still $< .10$ and not significant.

The second problem is that after ten years of follow-up, only 19 deaths from ischemic heart disease occurred. This small sample size is compounded by the fact that 15 of the 19 deaths occurred in nonsmoking women married to husbands who had stopped smoking at entry. Without more detailed characterization of these women's exposure to ETS, it is difficult to show an association between ETS and ischemic heart disease. As the study did not ascertain number of cigarettes smoked per day in former smokers, it is not

possible to measure any sustained effects of ETS in this former smoking group.

Another methodological problem is that wives of former smokers were grouped with wives of current smokers, and it is difficult to determine the exact effect of ETS for this former smoking group.

Although the Garland study does make an attempt in a prospective cohort study to measure the effects of possible exposure to ETS on ischemic heart disease, and does control for important cardiovascular confounders, such as obesity, blood pressure and cholesterol, the small sample size and the lack of adequate measurement of ETS in a former cigarette smoking group make the results only suggestive and certainly not definitive.

3. **Gillis.** The Gillis study (1989) consists of a prospective cohort comprised of men and women aged 45–64 years who resided in two towns, Renfrew and Paisley, in the west of Scotland, between 1972 and 1976. Residents (15,399) of these two towns who met the age and residency criteria (an 80% response) agreed to participate; 7,997 were subjected to a cardiorespiratory screening examination, a self-administered questionnaire that included questions on smoking behavior. The eventual sample was comprised of 3,960 men and 4,037 women where it was possible to study varying exposures to tobacco smoke by cohabitees. Four groups were established for analysis purposes:

1. Control—neither the case nor anyone living at the same address had ever smoked.
2. Presumed ETS exposure in the home—the case had never smoked but lived at the same address as a subject who had smoked.
3. Single smoking—the case was a smoker or an ex-smoker and lived at the same address as a person who had never smoked.
4. Double smoking: the case was a smoker or an ex-smoker who lived at the same address as a subject who was also a smoker or ex-smoker.

Mortality was used as an endpoint and was obtained from the National Health Service. Cardiovascular signs and symptoms were also noted. Data presented were complete through December 1985, for an average follow-up of 11.5 years.

The authors present relative risks and 95% confidence intervals adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol concentration and body mass index. Total mortality for ischemic heart disease was higher among those reportedly exposed to ETS in the home than controls.

Women with ETS exposure in the home were broken into two dose response categories for further analyses. These included: (1) the high exposure

group, where the woman's cohabitee smoked 15 or more cigarettes daily, and (2) the low exposure group where the women's cohabitee smoked less than 15 cigarettes daily. Age-adjusted mortality from ischemic heart disease was higher for those in the high exposure category than in the low exposure group.

Relative risk was adjusted for age, sex, social class and cardiovascular variables including diastolic blood pressure, serum cholesterol concentrations and body mass index. Compared with controls, the relative risk was 2.01 for ischemic heart disease and was not significant.

The Gillis paper has several methodological problems. The first is that it does not have sufficient power to demonstrate an association between ETS and ischemic heart disease. The sample size is too small.

A second problem is that the relative risk of 2.01 for ischemic heart disease for non-smokers compared with controls is too similar to the relative risk of 2.27 for active smokers compared with controls to make sense. An explanation for this is not clear, but may be due to small sample size as well.

Potential biases also exist in the Gillis study. One potential bias is that those exposed to ETS within the home may have had higher exposures to ETS outside of the home compared with controls. A second potential bias is misclassification of women as non-smokers when they may be former smokers or current smokers.

Although the Gillis study suggests an association between ETS and cardiovascular mortality in non-smokers, the data lacks any statistical significance. Also, the study reports some confusing and similar relative risks for active and passive smokers, and is confounded by several important methodological biases. This study should be replicated in a much larger study population, with adequate statistical power.

4. **Svendsen.** Svendsen (1987) reports the results of the Multiple Risk Factor Intervention Trial (MRFIT), conducted from 1973–1982. The trial consisted of men, aged 35–57, recruited from 18 cities in the United States. Males who fell within the upper 10–15% risk score distribution for heart disease, based on an index comprised of serum cholesterol concentration, cigarette smoking and diastolic blood pressure, and free of overt coronary heart disease were randomized to one of two groups: (1) special intervention or (2) usual care. Participants in both groups were seen annually over six to eight years for risk factor measurement and a medical examination. A detailed smoking history was obtained at baseline and at all subsequent annual visits. Cause of death was evaluated by a committee of three cardiologists after examination of death certificates and other medical records.

Fourteen hundred of 12,866 men reported that they had never smoked at entry into the study. Of these 1400, 1,245 were married. Of the later group, 286 were married to women who smoked and 959 were married to women who did not smoke.

The results compared ETS exposed husbands and non-ETS exposed husbands, where the husbands had *never* smoked. None of the endpoints showed statistical significance between the two groups, before or after adjustment for several variables, including age, baseline blood pressure, cholesterol, weight, alcohol consumption and education.

However, within the exposed group, increasing levels of cigarettes smoked daily by the wife had a statistically significant dose response relationship with husbands' CHD deaths. This is technically significant ($p = 0.04$) but is based on only one death in the 1–19 cigarettes smoked/day category.

A second analysis lumped never smoking husbands with ex-smoking husbands, calling these *non-smoking* husbands. This group was then evaluated on the basis of the smoking status of the wife. Non-smoking husbands of smokers did not show a statistically significant result when compared with husbands of non-smoking wives for mortality from CHD ($p = 0.15$) or from CHD itself as an endpoint ($p = .10$).

Several methodological problems exist in the Svendsen report. One problem is possible misclassification of husband's smoking status either at entry or subsequently. A second problem is that the wife's smoking status was based on interviews with the husband, and not on direct questioning of the wife.

There is also an alcohol-related bias, as MRFIT ETS-exposed husbands' had two drinks per week, on average, more than non-ETS exposed husbands, and this alcohol effect could explain the observed statistical significance in dose response.

Finally, by combining ex-smoking husbands with never smokers, Svendsen confounds any past effects of active smoking by the husband with exposure to ETS.

The MRFIT study serves as an exemplary prospective trial for its design and conduct. However, lack of statistical significance, failure to control for several confounding variables (such as alcohol consumption), misclassification, and misgrouping make it difficult to draw any conclusions from the study.

5. **Helsing.** The Helsing (1988) paper examines death certificates collected from July 1963 through July 1975 for a population living in July 1963 in Washington County, Maryland. This is based on underlying cause of death of arteriosclerotic heart disease including coronary disease (International Classification of Disease [ICD] −420) and other myocardial degeneration (ICD 422). As of July 15, 1963, 98% of the residents were asked questions that included information on sex, age, race, marital status, years of schooling, housing characteristics, information on cigarette, cigar and pipe smoking habits, as well as frequency of church attendance, for each household member aged 16.5 years or older.

Among 22,973 white men and 25,369 white women 25 years of age and

older in the 1963 census, 4,162 men and 14,873 women reported that they had never smoked. The 1971 follow-up population was a subset of these numbers: 3,454 men and 12,345 women.

The results showed that death rates from arteriosclerotic heart disease were higher among men (relative risk = 1.31) and women (relative risk = 1.24) who lived with smokers in 1963, after adjustment for age, marital status, years of schooling and quality of housing index. For women, relative risk increased significantly ($p < .005$) with increasing levels of exposure, but for men, there was little evidence of a dose response relationship.

Several methodological problems exist with the Helsing paper. The first major problem is that the only smoking data that was collected on every person was in 1963. Hence, no changes in smoking habits over the 12-year period were ascertained. In addition, no data were collected on other risk factors for heart disease such as diet, exercise, blood pressure and cholesterol. Finally, no ETS exposure outside the home was measured.

B. Case-Control Study

1. Lee. The Lee (1986) study is a case control (retrospective) study to evaluate the possible relationship between cigarette smoking and risk of lung cancer, chronic bronchitis, ischemic heart disease and stroke. The original questionnaire was administered in ten hospital regions in England, between 1977 and 1982. Although not recorded initially, ETS exposure data was subsequently collected in 1979 for married patients in the last four regions.

Two hundred cases and 200 matched controls were collected for each sex (male, female) and age (35–44, 45–54, 55–64, and 65–74) grouping to examine the possible relationship between ETS exposure and diagnosis of ischemic heart disease. Also matched were hospital region and, when possible, hospital ward and time of interview.

Ischemic heart disease cases and controls did not show a statistically significant difference in their exposure to ETS, based either on smoking habits of spouses or on an index accounting for exposure at home, at work, and during travel and leisure.

Although the Lee study is one of the few to attempt to examine nonspousal ETS exposure, it raises the general methodological issues that surround retrospective case control studies. In its finding of non-statistical significance for any trends of association between ETS and cardiovascular illness, the Lee paper confirms the need for execution of better controlled prospective trials.

C. Experimental Design

1. Aronow. The Aronow (1978) paper describes an experimental design to examine the possible relationship between exposure to ETS and exercise-induced angina in both a well ventilated and an unventilated room.

The design included ten men (eight non-smokers and two smokers) who exercised upright on a bicycle ergometer with a progressive work load until the onset of angina pectoris. Subjects were randomized to three groups: no smoking, smoking in a well ventilated room, or smoking in an unventilated room.

Aronow has suggested that the results of his study demonstrate that, under the conditions of the experiment, ETS exposure causes anginal pain to develop soon after exercise. In addition, the data from the study indicate that exposure to ETS causes an increase in carboxyhemoglobin, more after ETS exposure in an unventilated room than after ETS exposure in a ventilated room.

Several major criticisms of the Aronow study include: (1) the use of subjective pain as an end point without double blinding, (2) a very small sample size that can lead to a large variance based on just one or two subjects changing their responses, (3) problems associated with the Hawthorne effect [subjects tend to produce symptoms suggested to them], and (4) failure to control for stress.

D. *Conclusions*

The Surgeon General's Report of 1986 (1986) examined the studies of Hirayama, Gillis, Garland and Aronow, and concluded that "further studies on the relationship between involuntary smoking and cardiovascular disease are needed in order to determine whether involuntary smoking increases the risk of cardiovascular disease."

The National Research Council (1986) in 1986 reviewed the prospective studies of Garland, Gillis, Hirayama and Svendsen, as well as several experimental designs examining the biological plausibility of the association of ETS and cardiovascular disease, and concluded that:

> 1. No statistically significant effects of ETS exposure on heart rate or blood pressure were found in healthy men, women, and school-aged children during resting conditions. During exercise there is no difference in the cardiovascular changes for men and women between conditions of exposure to ETS and control conditions.
>
> 2. With respect to chronic cardiovascular morbidity and mortality, although biologically plausible, there is no evidence of statistically significant effects due to ETS exposure, apart from the study by Hirayama in Japan.

It is the opinion of this author that none of the studies critiqued in this paper provides any basis for altering the Surgeon General's and NAS's conclusions concerning ETS and cardiovascular disease.

This conclusion is reinforced by the findings of Schieveblein and Richter (1984). They report that, under real-life conditions, persons exposed to ETS inhale only approximately .02 to .01 of the amount of particulate matter

taken up by active smokers. Also, nicotine concentration in serum of ETS-exposed individuals is within a range that is barely distinguishable from the background level, and the increase in carboxyhemoglobin rarely exceeds 1%. The authors conclude that exposure to ETS "is not likely to have an effect on the development and progression of CHD."

II. Recommendations for Future Research

To provide meaningful recommendations for future research, it is necessary to evaluate the existing studies of ETS exposure and cardiovascular disease in light of the five criteria for causality discussed at the beginning of this paper.

The NAS concluded that a relationship between ETS exposure and cardiovascular disease is biologically plausible, and each of the studies reviewed in this paper appears to provide an adequate temporal association between ETS exposure (as measured by spousal smoking) and the onset of cardiovascular disease. However, the studies fail to meet one or more of the remaining criteria for causality.

Of the six studies concerning ETS exposure and cardiovascular morbidity and mortality, only two (Hirayama and Helsing) reported statistically significant relative risks for exposed compared to non-exposed populations, and neither study reported a relative risk greater than 2. Hirayama reported a dose dependent relationship but Helsing did not.

None of the studies demonstrate a specificity of association between ETS exposure and cardiovascular disease. Each of the studies fails to control for one or more important confounding variables, including lifestyle, blood pressure, serum cholesterol, obesity and socioeconomic status. None of the studies provides an accurate measurement of ETS exposure. All of the studies suffer from one or more serious methodological problems, including small sample size and possible misclassification of spousal smoking status. These confounding variables and methodological problems also preclude any demonstration of consistency of association among the existing studies.

In view of the inadequacy of existing studies, it is logical to consider whether the Framingham Heart Study might provide an adequate basis for a definitive evaluation of the relationship between ETS exposure and heart disease.

The Framingham Heart Study, initiated during 1948–1950, is comprised of a study cohort from a random subsample of the adult residents of Framingham, Massachusetts, of which 69% responded. No reports on ETS and heart disease have been published under the Study, but spousal smoking habits could be determined from the Study's data base. Although an effort could be made to measure ETS effects on heart disease in the Framingham Study, this would not be likely to provide an adequate basis for a definitive evaluation of ETS and heart disease.

The critical problem is that the Framingham Study does not provide a basis for an accurate measurement of ETS exposure, especially outside of the home. Use of data on spousal smoking habits as a surrogate for ETS exposure has been shown to present serious methodological and other problems in existing studies.

In any event, the recent paper by Seltzer (1989) suggests that the Framingham Study is not likely to show a significant association between ETS exposure and heart disease. Seltzer's paper compares the Surgeon General's statements regarding the association between active smoking and heart disease with the data in the Framingham Study. Seltzer points out that the Framingham data differ from the Surgeon General's conclusions in several important respects:

1. The Surgeon General asserts a four-fold greater CHD incidence in men who are heavy smokers as compared to non-smokers; Framingham reports relative risk ratios less than two.
2. The Surgeon General asserts that cigarette smoking among women has a predictive association with CHD; Framingham finds no such association.
3. The Surgeon General states there is an increase of CHD with increase of duration of smoking; in the Framingham Study, this increase is absent.
4. The Surgeon General claims that rates of CHD eventually are reduced in ex-smokers to those somewhere between smokers and non-smokers, and sometimes, after many years, falling to the level of non-smokers. The Framingham data are surprising in that reductions in CHD among ex-smokers is below levels for never smokers! This suggests that a selection bias may exist.

Given the relatively small effect of active smoking on heart disease reported in the Framingham Study, it appears unlikely that any effect of ETS exposure on heart disease could be measured under that Study.

In view of the lack of adequate existing data, future studies need to be performed that carefully examine the relationship between exposure to ETS and cardiovascular disease. It is the hope of this author that the critiques presented in this paper, examining many of the methodological problems associated with existing ETS epidemiological studies, will be of use to well-trained scientists. Familiarity with the five key points of causality in epidemiology is critical in designing studies that can clearly show whether any association exists between exposure to ETS and cardiovascular disease.

Based on the analysis in this paper, a meaningful future study should contain at least the following elements:

1. A representative sample large enough to yield adequate statistical power.
2. A design that provides control for important confounding variables, in-

cluding blood pressure, diet, alcohol consumption, plasma cholesterol, body weight, sex, socioeconomic status and exposure to environmental substances other than ETS.

3. A mechanism for accurate measurement of ETS exposure, including exposure outside the home, and adequate follow-up of exposure status.
4. A prospective design specifically developed to satisfy the criteria for causality.

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